COV

RESEARCH › RESEARCH SUMMARIES

Sharing our progress toward recovery

Research Summaries

Discover what the latest science from the RECOVER Initiative means for our ability to understand, diagnose, prevent, and treat **Long COVID**.

This page contains descriptions of findings from **RECOVER research studies**. These descriptions use plain language and a format that is easy to understand.

If you want to learn more about the scientific discoveries described here, you can also browse and search the complete list of **RECOVER Publications**.

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● OBSERVATIONAL ■ ADULT ◆ BROAD SYMPTOMS

◆ NEW-ONSET AND PRE-EXISTING CONDITIONS

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Vernon, SD; Zheng, T; Do, H; et al., *Journal of General Internal Medicine*

A new RECOVER study found that adults who had COVID-19 were more likely to develop a condition called myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) compared to those who didn't have COVID. ME/CFS can be very severe and similar to many forms of Long COVID. Even small amounts of effort can lead to days or weeks of physical and mental exhaustion in people with ME/CFS. Researchers studied about 13,000 RECOVER participants and found that 4.5% of people who had COVID in the study later developed ME/CFS, while only 0.6% of those who didn't have COVID got ME/CFS. These findings highlight the need for healthcare professionals to be aware that ME/CFS can develop after a COVID infection.

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● OBSERVATIONAL ■ ADULT ◆ RISK FACTORS ◆ VIRAL VARIANTS

Sex differences in Long COVID

Shah, DP; Thaweethai, T; Karlson, EW; et al.; RECOVER Consortium, *JAMA Network Open*

This RECOVER study looks at whether a person's sex at birth affects their risk of developing Long COVID. Researchers studied a large group of people with acute COVID-19, which is the early stage of the illness. They looked at factors like age, race, ethnicity, the COVID variant they had, and how severe their first infection was. They found that females were more likely to have Long COVID symptoms than males. Among females, the risk of getting Long COVID changed based on age, pregnancy status during a COVID infection, and if they had gone through menopause. Researchers discovered that the risk of getting Long COVID was higher in females ages

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why differences in sex at birth may put someone at higher risk of experiencing the long-term effects of COVID. Knowing this and understanding which hormones play a role in Long COVID risk could help researchers develop treatments and ways to prevent Long COVID that focus on sex at birth.

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● OBSERVATIONAL ■ ADULT ◆ BROAD SYMPTOMS ◆ RISK FACTORS

2024 update of the RECOVER-adult Long COVID research index

Geng, LN; Erlandson, KM; Hornig, M; et al., *JAMA*

Scientists updated a prior RECOVER study to explore Long COVID symptoms reported by participants in the RECOVER-Adult Observational Cohort Study. They compared symptoms in people who had COVID to those who did not to find the symptoms that were most different. The updated study included 13,647 participants, compared to 9,764 in the original, and added 8 new symptoms based on patient and community feedback. Symptoms that were most different between people with and without COVID infection include post-exertional malaise, fatigue, brain fog, dizziness, palpitations, smell or taste change, thirst, chronic cough, chest pain, shortness of breath, and sleep apnea. In addition, this research update classifies Long COVID symptoms into 5 groups of symptoms called clusters. The previous study focused on 4 clusters. This study update is important because it highlights the wide range of symptoms experienced by people with Long COVID. Understanding these symptoms will help researchers study Long COVID and look for treatments.

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EHR ADULT BROAD SYMPTOMS

Finding Long-COVID: Temporal topic modeling of electronic health records from the N3C and RECOVER programs

O'Neil, ST; Madlock-Brown, C; Wilkins, KJ; et al., *NPJ Digital Medicine*

In this RECOVER study, researchers wanted to find out which health conditions were common in people with long-term effects of COVID-19, known as Long COVID. They looked at the medical records of over 14 million patients who had and did not have COVID using a method called topic modeling. Topic modeling is a method to find patterns in groups of documents. Researchers used topic modeling to look at lists of health problems that millions of patients faced over time, including before and after they had COVID. This allowed them to find the conditions that were more common in people with Long COVID. Researchers found that health problems related to the lungs, heart, brain, and immune system were more common in people with Long COVID compared to those who didn't have Long COVID or had not had COVID. Common problems included chronic fatigue (feeling tired all the time), headaches, anxiety, and heart issues. They also found that some problems were more common in people of a certain age or sex (whether they are male or female). The study shows that Long COVID can affect many parts of the body and highlights how health problems can differ between groups. It also shows that age and sex can affect the chance of getting certain health conditions after COVID.

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Measurement of circulating viral antigens post-SARS-CoV-2 infection in a multicohort study

Swank, Z; Borberg, E; Chen, Y; et al., *Clinical Microbiology and Infection*

RECOVER researchers studied how COVID affects people over time. They wanted to know if parts of the SARS-CoV-2 virus (which causes COVID-19), called antigens, stay in people's blood long after a COVID infection. They also wanted to see if these antigens are linked to Long COVID. Long COVID is when a person has 1 or more symptoms that last for at least 3 months after getting COVID. First, the researchers took blood samples from adults who had COVID. These samples were taken a few days after getting sick and up to 14 months later. Then, they looked for 3 types of antigens that are usually in the blood after having COVID: the S1 subunit of the spike protein, the nucleocapsid protein, and the full-length spike protein. The full-length spike protein was the most common antigen found in adults who had COVID, especially in those who had blood taken between 4 and 7 months after getting COVID.

The study also looked at 34 common Long COVID symptoms, like trouble breathing, muscle pain, and brain fog. Many participants said that they had at least 1 Long COVID symptom for 1 month or more after getting sick. In the group with the most common kinds of symptoms, 2 out of 5 people had antigens in their blood. In the group without symptoms, about 1 out of 5 people had antigens in their blood. This study shows that the 3 antigens researchers found might be linked to Long COVID. People with symptoms were twice as likely to have these antigens in their blood for a long time. The results also show that parts of the SARS-CoV-2 virus can stay in the blood for up to 14 months after an infection. This is true for people who have long-term symptoms. But, it is also true in some people who do not have long-term symptoms.

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Prevalent metformin use in adults with diabetes and the incidence of Long COVID: An EHR-based cohort study from the RECOVER Program

Johnson, SG; Abedian, S; Stürmer, T; et al., *Diabetes Care*

Metformin is a drug that many doctors prescribe as treatment for type 2 diabetes mellitus (T2DM). Studies in the past have found that taking metformin before and during a COVID-19 infection helps lower the chances of getting very sick with COVID. These studies also found that taking metformin can lower the chance of a person being sick many months after getting COVID, which is called Long COVID. In this study, RECOVER researchers were interested in understanding if people with diabetes who were on different medications got Long COVID or died. They looked at electronic health records (EHRs), or computer-based versions of patient health records, for 88,342 adults with T2DM. The study looked at 2 groups. The first group used metformin to control their diabetes, while the second group used other medications to control their diabetes. The researchers found that the chances of getting Long COVID or dying were a little bit lower in the group that took metformin compared to the group taking other medications. Since being on metformin may help only a little bit with Long COVID for adults with T2DM, people taking diabetes medications do not need to change their treatment plans unless told by their doctor.

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REVIEW ADULT PEDIATRIC

Ethical considerations for enrolling "invested parties" in large-scale clinical studies: Insights from the RECOVER Initiative

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Many research centers have general formal guidelines about whether and how employees can participate in research studies. However, these guidelines don't always discuss the risks and benefits of researchers, staff, and community partners enrolling in studies they are involved in, which can create ethical questions. It is very important to consider these ethical questions for studies that aim to enroll large numbers of diverse participants.

All authors of this article are part of the Researching COVID to Enhance Recovery (RECOVER) Initiative, a large study enrolling participants at multiple locations across the country. They used what they learned from RECOVER to address what's currently missing from existing policy and ethics papers by creating a set of guidelines for how research studies can enroll researchers, staff, and community partners. The authors conclude that people should not be excluded from participating in their own research studies if certain requirements are met and there are rules to ensure everyone's safety.

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REVIEW ADULT

A case demonstration of the Open Health Natural Language Processing Toolkit from the National COVID-19 Cohort Collaborative and the Researching COVID to Enhance Recovery programs for a natural language processing system for COVID-19 or postacute sequelae

Wen, A; Wang, L; He, H; et al., *JMIR Medical Informatics*

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especially in the notes that doctors write during care. The researchers used a computer tool called Natural Language Processing (NLP) to find signs and symptoms of different conditions. However, NLP doesn't always work well, especially with new health problems like COVID or Long COVID, which are always changing. To improve this, researchers created a new NLP system that could collect detailed information about Long COVID signs and symptoms from EHRs. After testing the system at other medical sites, they found it worked well across different locations. The study showed that the new NLP system could successfully find the information they were looking for about COVID and Long COVID in EHRs. The NLP is now available to other researchers and is being used to collect information that can support additional studies on COVID and Long COVID.

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● OBSERVATIONAL ■ ADULT ◆ RISK FACTORS

Differentiation of prior SARS-CoV-2 infection and postacute sequelae by standard clinical laboratory measurements in the RECOVER cohort

Erlandson, KM; Geng, LN; Selvaggi, CA; et al., *Annals of Internal Medicine*

This RECOVER study looked at 25 different blood tests to see if any of the tests could be used to tell if someone might have Long COVID. Long COVID is when someone feels sick for a long time after having COVID-19. Researchers took blood from people who did and did not have COVID. They took blood from both groups 6 months after they got infected or after they joined the study. Researchers found small differences between the blood of people in each group. People who had COVID had slightly lower platelet counts (platelets help stop bleeding), a bit more sugar in

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tests could show if someone has Long COVID. This is because researchers could not tell if COVID caused the differences in the blood, or if they were there before people got sick.

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